NATIONAL GUIDELINE CLEARINGHOUSE™ (NGC) GUIDELINE SYNTHESIS

DIAGNOSIS AND MANAGEMENT OF UNCOMPLICATED LOWER URINARY TRACT INFECTION

GUIDELINES BEING COMPARED

1. **American College of Obstetricians and Gynecologists (ACOG)**. Treatment of urinary tract infections in nonpregnant women. Washington (DC): American College of Obstetricians and Gynecologists (ACOG); 2008 Mar. 10 p. (ACOG practice bulletin; no. 91). [51 references]
2. **Scottish Intercollegiate Guidelines Network (SIGN)**. Management of suspected bacterial urinary tract infection in adults. A national clinical guideline. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2006 Jul. 40 p. (SIGN publication; no. 88). [143 references]
3. **University of Michigan Health System**. Urinary tract infection. Ann Arbor (MI): University of Michigan Health System; 2005 May. 9 p. [10 references]

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AREAS OF AGREEMENT AND DIFFERENCE

A direct comparison of the American College of Obstetricians and Gynecologists (ACOG), Scottish Intercollegiate Guidelines Network (SIGN), and University of Michigan Health System (UMHS) recommendations for the diagnosis and treatment of uncomplicated LUTI in women is provided in the tables below.

Areas of Agreement

Diagnosis

The three groups agree that diagnosis of LUTI is based primarily on signs and symptoms and patient history. All of the groups recommend assessing for signs and symptoms of pyelonephritis, such as back pain or fever, as well as for vaginal symptoms (e.g., vaginal itch, discharge). There is further agreement that for patients with vaginal symptoms, alternative diagnoses should be considered and a pelvic examination performed.

All of the guidelines address empirical antibiotic treatment without performing diagnostic testing. SIGN explicitly recommends this for women with symptomatic LUTI. One exception to this recommendation pertains to women with limited signs and symptoms (no more than two), for whom SIGN recommends dipstick urinalysis be performed. UMHS acknowledges that empiric antibiotic treatment without any diagnostic testing may be appropriate in patients with a number of "classic" UTI symptoms, as the prior probability of UTI in these patients very likely exceeds 80%. They add, however, that if diagnostic testing is desired, dipstick UA (the cheapest and quickest test) should be performed first. According to ACOG, women with frequent recurrences and prior confirmation by diagnostic tests who are aware of their symptoms may be empirically treated without recurrent testing for pyuria. In women without a history of a laboratory-confirmed UTI, ACOG states that an office visit for urinalysis or dipstick testing is appropriate.

There is overall consensus that urine culture is not indicated in the vast majority of initial LUTI cases. The groups agree, however, that culture may be indicated in recurrent UTI, patients unresponsive to treatment, or in patients with complicating factors.

Treatment

There is overall agreement that while acute uncomplicated cystitis in women has historically been treated with longer (7-10 day) courses of antibiotics, recent data have demonstrated 3-day courses to be equally effective. Refer to Areas of Difference below for additional information.

Recurrent UTI

The two groups that address treatment of recurrent UTI, ACOG and UMHS, recommend treatment with a 3-day course of antibiotics. According to ACOG, a urine culture test of cure 1-2 weeks later to confirm clearance is suggested. UMHS notes that a follow-up urine culture can be performed if necessary to distinguish relapse from reoccurrence, but otherwise it is generally not necessary.

ACOG and UMHS agree that the first-line intervention for the prevention of the recurrence of LUTI is prophylactic or intermittent antimicrobial therapy. Both groups recommend either continuous prophylaxis with once-daily antibiotic treatment, or for women with recurrences associated with sexual activity, postcoital prophylaxis. They also agree that patient-initiated therapy, where women are given a prescription to fill when symptoms develop, can be recommended for women with recurrent UTI.

With regard to non-antibiotic interventions, all three groups agree that studies have found cranberry products to be useful for prophylaxis of recurrent UTI. An additional non-antibiotic intervention addressed by all three groups is estrogen therapy. None of the groups, however, explicitly recommends its use. According to ACOG, large, randomized trials are required before exogenous estrogen therapy can be conclusively recommended for UTI recurrence prevention. SIGN similarly notes that estrogens are not recommended for routine prevention of recurrent UTI in postmenopausal women. While UMHS states that vaginal estrogen can be considered in postmenopausal women, they also note that only poor data are available regarding the use of vaginal estradiol for UTI prophylaxis in postmenopausal women.

UTI in Pregnancy

SIGN and UMHS agree that pregnant women should be screened with urine culture at the first prenatal visit. SIGN further specifies that a positive culture should be confirmed with a second culture. Both guidelines agree that ASB should be treated with an antibiotic. SIGN does not specify the antibiotic to use; UMHS recommends a variety of FDA category B drugs. SIGN also recommends treatment of symptomatic bacteriuria in pregnant women with antibiotics (unspecified), whereas UMHS does not address this topic. However, for symptomatic cystitis in pregnancy, UMHS recommends treatment and follow-up similar to that for ASB.

Areas of Difference

Treatment

Recommendations regarding antibiotic therapy differ. While both ACOG and UMHS recommend TMP/SMX twice daily for 3 days as first-line treatment, SIGN recommends 3 days of either TMP alone or nitrofurantoin.

With regard to second line therapies, ACOG states that other medications that have shown equivalency to TMP/SMX include 3 days of TMP alone and the fluoroquinolones ciprofloxacin, levofloxacin, norfloxacin, and gatifloxacin. UMHS also recommends 3 days of quinolones as a second line treatment. In contrast to ACOG and UMHS, SIGN states that quinolones should not be used for empirical treatment of LUTI. According to SIGN, there is there is no clear first choice alternative to TMP or nitrofurantoin. Recommendations regarding other second-line therapies differ as well. UMHS recommends 7 days of amoxicillin and first-generation cephalosporins as second-line therapies. ACOG, on the other hand, does not include beta-lactam antibiotics in its list of recommended antimicrobial regimens, stating that beta-lactams, such as first-generation cephalosporins and amoxicillin, are less effective in the treatment of uncomplicated acute cystitis than the antimicrobials they recommend.

While nitrofurantoin is not recommended as a first-line therapy by either ACOG or UMHS, both groups do recommend it as a second-line therapy. The recommended duration of nitrofurantoin differs, however, with ACOG and UMHS recommending 7 days and SIGN recommending 3 days. Although SIGN notes that the Infectious Diseases Society of America (IDSA) recommends 7 days of treatment with nitrofurantoin, SIGN states there is no direct evidence comparing 3-day therapy with 7-day therapy.

Recurrent UTI

The two groups that address methenamine hippurate, ACOG and SIGN, differ in their recommendations for its use. According to SIGN, it may be used to prevent symptomatic UTI in patients without known upper renal tract abnormalities. ACOG, on the other hand, states that a meta-analysis reviewing 11 trials using methenamine hippurate found that, although well tolerated, there was not enough evidence to conclusively support its use for UTI prophylaxis.

Treatment via Telephone

According to UMHS, many women can be assessed and safely managed without the need for an office visit or laboratory test. UMHS also points out that one study found telephone triage and management lowered costs, increased the appropriate use of antibiotics, and did not lead to an increase in adverse outcomes. SIGN, on the other hand, explicitly recommends against telephone management, stating that it cannot be recommended as an alternative to standard consultation. SIGN's conclusion is based in part on the same study by Saint et al., cited by UMHS, which showed an increase in return visits for STDs after nurse telephone consultation. SIGN's other reason for recommending against telephone consultation is that a Department of Health advisory recommends limiting antibiotic prescribing over the telephone.

COMPARISON OF RECOMMENDATIONS	
UTI IN NON-PREGNANT WOMEN **Abbreviations** **Back to TOC**	
Diagnosis	
ACOG (2008)	***The following conclusion is based on limited or inconsistent evidence (Level B)***: • The initial treatment of a symptomatic lower UTI with pyuria or bacteriuria or both does not require a urine culture. ***The following conclusions are based primarily on consensus and expert opinion (Level C)***: • To diagnose bacteriuria, decreasing the colony count to 1,000-10,000 bacteria per milliliter in symptomatic patients will improve the sensitivity without significantly compromising specificity. **Diagnosis** **Clinical History and Examination** Acute bacterial cystitis usually presents clinically as dysuria, with

symptoms of frequent and urgent urination, secondary to irritation of the urethral and bladder mucosa. Women also may experience suprapubic pain or pressure and rarely have hematuria. Fever is uncommon in women with uncomplicated lower UTI. Acute urethritis secondary to infection from *Neisseria gonorrhoeae* and *Chlamydia trachomatis* or pain secondary to genital herpes simplex virus type 1 and herpes simplex virus type 2 may occur with similar clinical symptoms and should be ruled out.

Laboratory Evaluation

Bacteriuria is diagnosed using a clean-voided midstream urine sample. Traditionally, 100,000 single isolate bacteria per milliliter has been used to define significant bacteriuria, with excellent specificity, but a sensitivity of 50%. To diagnose bacteriuria, decreasing the colony count to 1,000-10,000 bacteria per milliliter in symptomatic patients will improve the sensitivity without significantly compromising specificity. Urine dipstick testing for LE or nitrite is a rapid and inexpensive method with a sensitivity of 75% and specificity of 82%. It is a good screening test, but women with negative test results and symptoms should still have a urine culture or urinalysis or both performed because false-negative results are common. A standard urinalysis will detect pyuria, defined as 10 leukocytes per milliliter, but pyuria alone is not a reliable predictor of infection. However, pyuria and bacteriuria together on microscopic examination results markedly increases the probability of UTI. The use of a postvoid residual volume measure, urodynamic testing, cystourethroscopy, or radiologic imaging is not cost-effective in women unless they have evidence of a complicated infection or renal calculi. These are rarely necessary to diagnose acute uncomplicated cystitis and pyelonephritis.

Is empiric treatment of urinary tract infection without performing urinalysis appropriate?

It is a common practice among primary care physicians to empirically treat women with symptoms of a lower UTI without performing laboratory analyses. It has been considered a cost-effective strategy, decreasing the number of diagnostic tests and office visits. However, many women, especially postmenopausal women, without a laboratory-proven UTI have symptoms of intermittent dysuria or urgent or frequent urination. Empiric treatment of these women leads to unnecessary antibiotic use and the development of antimicrobial resistance. Testing for pyuria, by urinalysis or by urinary dipstick testing, improves the likelihood of identifying infection by 25% or more. Thus, in women without a history of a laboratory-confirmed UTI, an office visit for urinalysis or dipstick testing is appropriate. Women with frequent recurrences and prior confirmation by diagnostic tests who are aware of their symptoms may be empirically treated without recurrent testing for

	pyuria. ***When is urine culture necessary?*** The initial treatment of a symptomatic lower UTI with pyuria or bacteriuria does not require a urine culture. However, if clinical improvement does not occur within 48 hours or in the case of recurrence, a urine culture is useful to help tailor treatment. A urine culture should be performed in all cases of upper UTIs.
SIGN (2006)	**Tests for Bacteriuria or Pyuria Do Not Establish the Diagnosis of UTI** • The diagnosis of UTI is primarily based on symptoms and signs. • Tests that suggest or prove the presence of bacteria or white cells in the urine may contribute additional information to inform management but rarely have important implications for diagnosis. **Routine Urine Culture Is Not Required to Manage LUTI in Women** • Women with symptomatic LUTI should receive empirical antibiotic treatment. • All urine samples taken for culture will be from patients that are not responding to treatment and will bias the results of surveillance for antibiotic resistance. **<u>Management of Bacterial UTI in Adult Women</u>** **Diagnosis** **C** - In otherwise healthy women presenting with symptoms or signs of UTI, empirical treatment with an antibiotic should be considered. **C** - In women with symptoms of vaginal itch or discharge, explore alternative diagnoses and consider pelvic examination. **Good Practice Point**: In patients presenting with symptoms or signs of UTI who have a history of fever or back pain, the possibility of UUTI should be considered. Empirical treatment with an antibiotic should be started and urine culture performed to guide the choice of antibiotic. **Near Patient Testing** Near patient tests may include the appearance of the urine sample, microscopy and testing by means of dipsticks.

	Urine Microscopy **Good Practice Point**: Urine microscopy should not be undertaken in clinical settings in primary or secondary care. *Dipstick Tests* **B** - Dipstick tests should only be used to diagnose bacteriuria in women with limited symptoms and signs (no more than two symptoms). • Women with limited symptoms of UTI who have negative dipstick urinalysis (LE or nitrite) should be offered empirical antibiotic treatment. • The risks and benefits of empirical treatment should be discussed with the patient and managed accordingly. • If a woman remains symptomatic after a single course of treatment, she should be investigated for other potential causes. **Good Practice Point**: In elderly patients (over 65 years of age), diagnosis should be based on a full clinical assessment, including vital signs.
UMHS (2005)	**NGC Note**: An algorithm is provided in the original guideline document for the diagnosis and management of UTI. **Diagnosis** • **History**. Diagnosis is made primarily by history. In women with dysuria and frequency, in the absence of vaginitis, the diagnosis is UTI 80% of the time *[C]*. • **Phone triage**. In women with prior history of uncomplicated UTIs, consider phone triage *[C]*. • **Urinalysis**. Urinalysis for detection of pyuria by dipstick or microscope has a sensitivity of 80 to 90% and a specificity of 50% for predicting UTI *[B]*. • **No urine culture**. Urine culture is NOT indicated in the vast majority of UTIs. UC has a sensitivity of 50% (if threshold for positive is >105 organisms); sensitivity can be increased to >90% if threshold is >102 organisms *[C]*. Consider urine culture only in recurrent UTI or in the presence of complicating factors. **Summary of diagnostic approach**. The diagnostic evaluation for UTI therefore begins with an estimation of prior probability of UTI based on the patient's symptoms. From the preceding, it is clear that presence of vaginal symptoms necessitates pelvic examination; however, in the absence of vaginal symptoms, vaginitis is very uncommon and pelvic examination is unnecessary. One caveat: the physician, nurse practitioner or triage nurse should be wary of anything in the patient's history that would increase the risk for

	sexually transmitted infection, as this may call for pelvic examination as well. Beyond performing a pelvic examination in patients for whom it is indicated, no formal physical exam is needed, unless the patient has complaints suggestive of pyelonephritis (see that section of the original guideline document). With a number of "classic" UTI symptoms, the prior probability of UTI very likely exceeds 80% and may in fact exceed the predictive usefulness of either dipstick urinalysis or urine microscopy. Therefore, it may be appropriate to simply treat a patient with classic UTI symptoms without any diagnostic testing. If diagnostic testing is desired, dipstick UA (the cheapest and quickest test) should be performed first. If this confirms a high likelihood of UTI, no further testing need be done, and treatment can be initiated. If dipstick UA is equivocal, possible next steps would be to perform a pelvic exam, perform urine microscopy, and/or defer treatment and send urine for culture.
Treatment	
ACOG (2008)	***The following recommendations and conclusions are based on good and consistent scientific evidence (Level A)***: • Screening for and treatment of ASB is not recommended in nonpregnant, premenopausal women. • Resistance rates higher than 15-20% necessitate a change in antibiotic class. • A 3-day antimicrobial regimen is the preferred treatment duration for uncomplicated acute bacterial cystitis in women, including women aged 65 years and older. ***The following conclusions are based primarily on consensus and expert opinion (Level C)***: • Beta-lactams, such as first-generation cephalosporins and amoxicillin, are less effective in the treatment of acute uncomplicated cystitis than those antimicrobials listed below. <u>Treatment Regimens for Uncomplicated Acute Bacterial Cystitis</u> **Note**: Refer to Table 1 of the original guideline document for dosages and adverse events • TMP/SMX • TMP • Ciprofloxacin • Levofloxacin

- Norfloxacin
- Gatifloxacin
- Nitrofurantoin macrocrystals
- Nitrofurantoin monohydrate macrocrystals
- Fosfomycin tromethamine

General Principles of Treatment

Uncomplicated Acute Bacterial Cystitis

In the past, uncomplicated acute cystitis has been treated with 7-10 days of antimicrobial therapy. However, recent data have shown that 3 days of therapy is equivalent in efficacy to longer duration of therapy, with eradication rates exceeding 90%. Recommended agents for the 3-day therapy are detailed above (see "Treatment Regimens for Uncomplicated Acute Bacterial Cystitis"). Of note, beta-lactams, such as first-generation cephalosporins and amoxicillin, are less effective in the treatment of uncomplicated acute cystitis than those antimicrobials listed above (see "Treatment Regimens for Uncomplicated Acute Bacterial Cystitis"). This is because of increasing resistance among the common uropathogens, rapid excretion from the urinary tract, and the inability to completely clear gram-negative rods from the vagina, increasing the risk for recurrence.

How should uncomplicated acute bacterial cystitis in women be treated?

A 3-day antimicrobial regimen is now the recommended treatment for uncomplicated acute bacterial cystitis in women, with bacterial eradication rates consistently higher than 90%. Table 1 in the original guideline document (see "Treatment Regimens for Uncomplicated Acute Bacterial Cystitis" above) lists the current recommended regimens for treatment, both 3-day and 7-day courses.

Use of TMP-SMX for 3 days is considered the preferred therapy, with a 94% bacterial eradication rate. However, in areas where resistance to this antimicrobial agent exceeds 15-20%, another one of the listed regimens should be chosen. The other medications that have shown equivalency include TMP alone, ciprofloxacin, levofloxacin, norfloxacin, and gatifloxacin.

The fluoroquinolones, although highly effective, should not be used as a first-line agent in areas where resistance prevalence to TMP-SMX is low – currently resistance to the fluoroquinolones is uncommon, and overuse will likely hinder the ability to effectively use this class of antimicrobials in patients with complicated UTIs and those patients with respiratory and other non-UTIs. Most experts now agree that use of sulfonamides, ampicillin, and amoxicillin is

	less effective than use of TMP-SMX and the fluoroquinolones (see previous section) and should not be used as first-line therapy. Use of nitrofurantoin, a drug frequently used in the pregnant population, is not well studied in nonpregnant women with acute cystitis. It is not recommended for use in a 3-day regimen but has been found to be effective in a 7-day antimicrobial regimen and is listed above (see "Treatment Regimens for Uncomplicated Acute Bacterial Cystitis"). Resistance to nitrofurantoin remains low (less than 5%). The low prevalence of resistance and its ability to concentrate in urine continue to make nitrofurantoin a useful medication in the treatment of uncomplicated cystitis, particularly in areas where resistance rates to the first-line medications are high. It is ineffective against *Proteus mirabilis*. Of note, nitrofurantoin can rarely induce hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency, and use should be avoided in these patients. Compared with the nitrofurantoin macrocrystal formulation, which requires frequent dosing (four times per day) and has a high likelihood of gastrointestinal side effects, monohydrate macrocrystal formulation is given twice daily, so side effects occur less frequently.
SIGN (2006)	**Antibiotic Treatment** *Symptomatic Bacteriuria, LUTI* **A** - Non-pregnant women with symptoms or signs of acute LUTI, and either high probability of or proven bacteriuria, should be treated with antibiotics. Three to six days of antibiotic treatment for uncomplicated LUTI in women aged 60 or over is as effective as treatment for 7 to 14 days. Guidelines from the IDSA and Health Protection Agency (HPA) recommend three days treatment with TMP for LUTI. There is more direct evidence for three days treatment with co-trimoxazole, but it is reasonable to infer that TMP is equally effective as co-trimoxazole. Three days of treatment with nitrofurantoin has been shown to be effective in non-pregnant adult women with uncomplicated UTI. The IDSA recommends seven days treatment with nitrofurantoin. There is no direct evidence comparing three days nitrofurantoin with seven days nitrofurantoin. **B** - Non-pregnant women of any age with symptoms or signs of acute LUTI should be treated with TMP or nitrofurantoin for three days. **Good Practice Point**: Women with renal impairment should not be

	treated with nitrofurantoin as: • An effective concentration of antibiotic in the urine is not achievable • A toxic concentration of antibiotic can occur in the plasma **D** - Women with LUTI, who are prescribed nitrofurantoin, should be advised not to take alkalinising agents (such as potassium citrate). Resistance is increasing to all of the antibiotics used to treat UTI, and there is no clear first choice alternative to TMP or nitrofurantoin. **B** - Patients who do not respond to TMP or nitrofurantoin should have urine taken for culture to guide change of antibiotic. **Good Practice Point**: Quinolones should not be used for empirical treatment of LUTI. *Telephone Consultation* Although telephone consultation and antibiotic prescribing by nurse practitioners could be a cost-effective alternative to a general practitioner visit it goes against one of four key recommendations made to primary care by the Department of Health, Standing Medical Advisory Committee, which was to "limit antibiotic prescribing over the telephone." The available evidence also raises serious questions about the safety of telephone consultations for excluding STDs. Telephone consultation cannot be recommended as an alternative to a standard consultation.

UMHS (2005)	**NGC Note**: An algorithm is provided in the original guideline document for the diagnosis and management of UTI.
	
	Treatment
	
	• **First line**: three days of TMP/sulfa *[A]*.
	• **Second line**:
	  • Three days of quinolone (contraindicated in pregnancy) *[A]*.
	  • Seven days of nitrofurantoin, amoxicillin, first-generation cephalosporin *[A]*.
	
	Follow-up
	
	• No tests if asymptomatic. No laboratory follow-up is necessary if asymptomatic *[B]*.
	
	Treatment. Acute uncomplicated cystitis in women historically has been treated with longer (7-10 day) courses of antibiotics. More

	recent studies have found shorter courses (3-5 days) of oral antibiotics to be as effective as traditional courses. A review of 28 treatment trials of adult women with uncomplicated cystitis concluded that no benefit was achieved by increasing the length of therapy beyond 5 days. The advantages of shorter course therapy include decreased costs of antibiotics, improved patient compliance and decreased adverse effects of antibiotic treatment (e.g., amoxicillin associated vaginitis). When comparing the different treatment strategies, single dose regimens are less efficient at eradicating bacteriuria than 3-5 day regimens (23-81% versus 77-91% long-term cure, respectively). Beta-lactam antibiotics are more effective, with cure rates of 77 to 92%, if given greater than 5 days. Similarly longer courses of 7 days for nitrofurantoin are recommended. There appears to be no benefit in increasing the duration of TMP/SMX or TMP beyond 3 days; cure rates of 82 to 85% have been achieved with 3-day therapy. Adverse effects increase markedly if treatment is continued past 3 days. Of the 3-day regimens, TMP/SMX is more effective and less expensive than nitrofurantoin, cefadroxil, or amoxicillin for treatment of uncomplicated cystitis in women. Quinolones have also been shown to be effective in 3-day courses; however, cost is increased significantly over TMP combinations. Ciprofloxacin, 100 mg BID for 3 days, appears to be the most cost effective quinolone regimen/SMX. Fluoroquinolones increase the risk of tendon rupture in those over age 60, in kidney, heart, and lung transplant recipients, and with use of concomitant steroid therapy. Therefore, the optimal treatment of uncomplicated UTI in patients who are not allergic or sensitive is 3-days of TMP/SMX. Longer courses of therapy should be used in women who are diabetic, pregnant (quinolones contraindicated), have had symptoms longer than 7 days, or have other evidence for complicated UTI (see Table 2). In general, older women with lifelong history UTI and no history of complicating factors are managed as uncomplicated UTI. However, specific treatment algorithms in this age group have rarely been assessed. While 3-days of TMP/SMX is the first line in older women (>65 years), consider 7-days of TMP/SMX or 3-days of ciprofloxacin for those whose health status increases risk of urological defects.
RECURRENT UTI **Abbreviations** **Back to TOC**	
ACOG (2008)	**Recurrent UTI** Management of recurrent UTIs should start with a search for known risk factors associated with recurrence. These include frequent intercourse, long-term spermicide use, diaphragm use, a new sexual partner, young age at first UTI, and a maternal history of UTI.

Behavioral changes, such as using a different form of contraception instead of spermicide, should be advised. Antimicrobial treatment of recurrent UTIs is based on patient desire and frequency of recurrences. A 3-day course of one of the antimicrobial regimens listed below is started to clear the infection. A urine culture test of cure 1-2 weeks later to confirm clearance is suggested.

Treatment Regimens for Uncomplicated Acute Bacterial Cystitis

Note: Refer to Table 1 of the original guideline document for dosages and adverse events

- TMP/SMX
- TMP
- Ciprofloxacin
- Levofloxacin
- Norfloxacin
- Gatifloxacin
- Nitrofurantoin macrocrystals
- Nitrofurantoin monohydrate macrocrystals
- Fosfomycin tromethamine

For women with frequent recurrences, continuous prophylaxis with once-daily treatment with nitrofurantoin, norfloxacin, ciprofloxacin, TMP, TMP/SMX, or another agent listed above has been shown to decrease the risk of recurrence by 95%. This can be continued for 6-12 months and then reassessed. Women with recurrences associated with sexual activity may benefit from postcoital prophylaxis–a single dose of one of the agents listed above, taken after sexual intercourse, is effective in decreasing recurrences.

Patient-Initiated Therapy

Many women with recurrent UTIs are aware of symptom onset. As the cost of office and hospital emergency room visits continues to increase, patient-initiated therapy has become a viable option for treatment. Women are given a prescription for one of the 3-day dosage regimens listed in above (see "Treatment Regimens for Uncomplicated Acute Bacterial Cystitis") and should be instructed to start therapy when symptoms develop. Some clinicians also will give the women urine dipsticks and use pyuria as well as symptoms as an indication to initiate treatment. If symptoms do not improve in 48 hours, clinical evaluation should be performed. Patient-initiated therapy has been found to be safe, effective, and economical.

How effective are interventions to prevent recurrence of cystitis?

The first-line intervention for the prevention of the recurrence of cystitis is prophylactic or intermittent antimicrobial therapy, as discussed previously. Recurrences are prevented in 95% of cases.

	However, multiple other nonmedical and medical interventions have been suggested. There is little evidence that aggressive hydration to prevent recurrences has any major effect, and this practice can theoretically worsen urinary retention issues, decrease urinary pH affecting the antibacterial activity of urine itself, and dilute antimicrobial concentrations in the urinary tract. It currently is not recommended for prevention of UTI recurrence. Likewise, postcoital voiding has not been proved effective, nor have douching or wiping techniques. The benefit of vaginal lactobacilli application also remains unproven. Drinking cranberry juice has been shown to decrease symptomatic UTIs. This is because of the proanthocyanidin-inhibiting attachment of urinary pathogens to the urinary tract epithelial cells. In a recent meta-analysis addressing the effectiveness of drinking cranberry juice and taking other formulations, it was reported that taking cranberry formulations was more effective compared with taking placebo. In one of the studies in the meta-analysis, it was reported that both drinking cranberry juice and taking cranberry tablets significantly decreased the number of women with at least one symptomatic UTI per year to 18% and 20%, respectively, compared with 32% for those taking placebo. However, there are insufficient data to determine the length of therapy and the concentration required to prevent recurrence long term. Methenamine salts (methenamine hippurate and methenamine mandelate) have long been used for the prevention of UTI. They produce formaldehyde, which acts as a bacteriostatic agent. In a meta-analysis reviewing 11 trials using methenamine hippurate, it was found that, although well tolerated, there was not enough evidence to conclusively support this use for urinary prophylaxis. Recurrence rates are high among postmenopausal women. The hypoestrogenic state with associated genitourinary atrophy likely contributes to the increased prevalence. Oral and vaginal exogenous estrogens have been studied with varying results. Estrogen-releasing pessaries and rings have had some success in decreasing UTI recurrences, as have topical estrogen creams. Although in one study a benefit from oral estrogen therapy was found, in other larger studies no reduction in UTI frequency in postmenopausal women receiving oral estrogen was shown. Large, randomized trials are required before exogenous estrogen therapy can be conclusively recommended for UTI recurrence prevention. Vaginal mucosal vaccines have been proposed to improve long-term resistance to recurrent UTIs. Vaccine targets include the Type I and Type II pili. One study has shown some promise, but currently no vaccines are available for clinical use.
SIGN (2006)	**Non-Antibiotic Treatment**

	Cranberry Products **A** - Women with recurrent UTI should be advised to take cranberry products to reduce the frequency of recurrence. **Good Practice Point**: Women should be advised that cranberry capsules may be more convenient than juice and that high strength capsules may be most effective. There is no evidence to support the effectiveness of cranberry products for treating symptomatic episodes of UTI. **D** - Patients taking warfarin should avoid taking cranberry products unless the health benefits are considered to outweigh any risks. **Good Practice Point**: Increased medical supervision and international normalized ratio (INR) monitoring should be considered for any patient taking warfarin with a regular intake of cranberry products. **Good Practice Point**: Women with recurrent UTI should be advised that cranberry products are not available on the National Health Service (NHS) but are readily available from pharmacies, health food shops, herbalists and supermarkets. *Methenamine Hippurate* **B** - Methenamine hippurate may be used to prevent symptomatic UTI in patients without known upper renal tract abnormalities. *Oestrogen* **A** - Oestrogens are not recommended for routine prevention of recurrent UTI in postmenopausal women. Treatment with oestrogens may be appropriate for some women. *Analgesia* **Good Practice Point**: Women with uncomplicated UTIs may wish to use over the counter remedies to try and relieve symptoms.
UMHS (2005)	**Follow-Up** **For recurrent UTIs**. In patients with recurrent UTIs (>3/year): • Consider prophylaxis/self-initiated therapy *[A]* • Urologic structural evaluation rarely indicated *[D]*

Management Summary for Recurrent UTIs

1. **Treat acute UTI** (Table 3 in the original guideline document).
2. **Follow-up urine culture**. Check follow-up urine culture if necessary to distinguish relapse from reoccurrence, otherwise generally not necessary.
3. **Educate**. Counsel about reinfection:
    - Use of diaphragm or spermicide - consider alternative
    - Postcoital voiding
    - Consider vaginal estrogen in postmenopausal women
4. **Prophylaxis**. Consider:
    - Continuous or postcoital (TMP/sulfa SS, Macrodantin 100 mg)
    - Self initiated therapy (Table 3 in the original guideline document)
5. **No structural evaluation**. Structural evaluation is generally not indicated.

Recurrent UTIs

Treatment. Most women with recurrent UTIs respond to recommended antibiotics regimens (see Table 3 in the original guideline document). Persistent bacteriuria or early clinical reoccurrence should raise the possibility of relapse. These patients can be identified by early positive post therapy cultures with sensitivities showing "sensitive" to the agent used to treat them. Patients with documented relapse should be treated with prolonged courses of antibiotics (2 to 6 weeks) with follow-up urine cultures to document sterility. Consideration should then be made for prophylactic therapy. One should also have a somewhat lower threshold for urologic structural evaluation.

The vast majority of women with uncomplicated recurrent UTIs experience reinfection. They will respond clinically and bacteriologically to three day courses of antibiotic therapy. These women rarely have any urologic structural abnormality causing the recurrent reinfections, and structural evaluation is therefore not indicated. Patients should be counseled about risk factors for UTIs (diaphragm use, spermicide use, atrophic vaginitis in postmenopausal women, not emptying the bladder after intercourse). Post therapy urine cultures should occasionally be checked in women with recurrent UTIs to differentiate relapse from reinfection, but in general are not necessary. In women with recurrent UTIs due to reinfection prophylactic or self-initiated therapy should be considered.

Prophylaxis of Recurrent UTIs

Recurrent UTI is defined as 3 or more episodes of UTI over the past 12 months, or 2 UTIs in the past 6 months. Prophylaxis may be possible using antibiotics or other methods. The decision to use

	prophylaxis or not, and which agent to use, should be made jointly by the physician and patient, taking into account the individual preferences of each woman. Prophylactic antibiotic use, either daily or used only postcoitally, has been shown to reduce frequency of UTI in sexually active women. The benefits accrue only during active prophylaxis. Once antibiotics are discontinued, UTIs occur at the same rate as in placebo-treated sexually active women. Adverse events from antibiotic use are generally mild, although women vary in their evaluation of the impact of various side effects (i.e., oral or vaginal candidiasis may be seen as a severe side effect by some, mild by others.) Commonly used prophylactic antibiotics include cotrimoxazole, nitrofurantoin, cephalexin, or a quinolone. Nitrofurantoin appears to have the highest withdrawal rate, followed by cephalexin. It appears that post-coital prophylaxis is as effective as daily intake. Quinolones should be avoided, given concerns about antibiotic resistance, as well as higher cost. When used, they may be considered for weekly dosing. They are contra-indicated in pregnancy. In regards to the use of other prophylactic measures, some studies have shown that cranberry juice or cranberry tablets can significantly reduce the annual incidence of UTIs in sexually active women with a history of recurrent UTIs *[A]*. The best dose is unknown, but one trial suggests that tablets are equally as effective as juice, and cost less. No trials that suggest cranberry in any form is useful in the treatment of UTI. Only poor data are available regarding the use of vaginal estradiol for UTI prophylaxis in postmenopausal women.
UTI IN PREGNANCY **Abbreviations** **Back to TOC**	
ACOG (2008)	No recommendations offered.
SIGN (2006)	**Diagnosis of UTI in Pregnant Women** *Near Patient Testing* **A** - Standard quantitative urine culture should be performed routinely at first antenatal visit. **A** - The presence of bacteriuria in urine should be confirmed with a second urine culture. **A** - Dipstick testing should not be used to screen for bacterial UTI at

first or subsequent antenatal visits.

Good Practice Point: Dipsticks to test only for proteinuria and the presence of glucose in the urine should be used for screening at the first and subsequent antenatal visits as a more cost-effective alternative to multi-reagent dipsticks that detect the presence of nitrite, leukocyte esterase and blood in addition to protein and glucose.

Screening During Pregnancy

C - Women with bacteriuria confirmed by a second urine culture should be treated and have repeat urine culture at each antenatal visit until delivery.

Good Practice Point: Women who do not have bacteriuria in the first trimester should not have repeat urine cultures.

Management of Bacterial UTI in Pregnant Women

Symptomatic Bacteriuria

B - Pregnant women with symptomatic UTI should be treated with an antibiotic.

Good Practice Points:

A single urine sample should be taken for culture before empiric antibiotic treatment is started.

Refer to local guidance for the safest, cheapest, effective antibiotic for pregnant women.

Given some antibiotics are toxic in pregnancy, refer to the British National Formulary (BNF) for contraindications.

Given the risks of symptomatic bacteriuria in pregnancy, a urine culture should be performed seven days after completion of antibiotic treatment as a test of cure.

ASB

A - ASB detected during pregnancy should be treated with an antibiotic.

Good Practice Point: Refer to local guidance for the safest, cheapest, effective antibiotic for pregnant women.

	Screening During Pregnancy **C** - Women with bacteriuria confirmed by a second urine culture should be treated and have repeat urine culture at each antenatal visit until delivery.
UMHS (2005)	**UTI in Pregnancy** **ASB**. Screening for ASB is recommended for pregnant women at the first prenatal visit. Urine culture is an appropriate screening tool. Clean catch urine analysis is recognized as appropriate by the American College of Obstetricians and Gynecologists. Treatment of ASB can be accomplished with a variety of FDA category B drugs, including amoxicillin, cephalosporins, nitrofurantoin and TMP/SMX. Quinolones should generally not be used during pregnancy (FDA category C). A seven-day course is recommended with follow-up urine cultures to document sterile urine. Persistent bacteriuria requires retreatment guided by sensitivities and then consideration of suppressive therapy, usually with nitrofurantoin. **Symptomatic cystitis in pregnancy**. Symptomatic cystitis in pregnancy, although rare, should be treated and followed-up similarly to asymptomatic bacteria.
EDUCATION Abbreviations Back to TOC	
ACOG (2008)	No recommendations offered.
SIGN (2006)	**General Advice** Healthcare professionals should offer: • Information on cranberries. Patients should be advised that further research is required to determine the best way to take cranberries, for example, juice, tablets, or a combination; in what concentration; routinely or preventatively; and how often. • Advice on "complicated" versus "uncomplicated" infections. The distinction between a 3-day versus a 7-day course of pills and the reasons for using one or the other should also be explained to the patient. These issues could affect concordance. • Contraception advice. This and the role of sexual activity is a critical issue for women, and one which may affect concordance. This issue should be explicitly dealt with by healthcare professionals prescribing and dispensing treatment. • A reminder to patients and carers that the presence of

	bacteriuria does not always indicate disease. Especially in elderly patients, ASB is a normal condition and should not be treated with antibiotics.
UMHS (2005)	**Information the Patient Needs to Know** • **Cause**. UTI are caused by bacteria and require antibiotic treatment. • **Complete treatment**. Antibiotic must be taken for the full prescribed duration, even if symptoms disappear. • **Fluids**. You should drink at least 8 glasses of fluids per day to help flush the urinary system. • **Possible side effects of treatment**. Side effects of antibiotics include rash, nausea, diarrhea, and vaginitis. If your doctor prescribes a urinary analgesic, phenazopyridine (Pyridium), to help with pain, it may turn your urine an orange color. • **Call for early follow-up**. Symptoms that require early follow-up included: persistent fever or discomfort persisting greater than 72 hours after starting therapy, inability to take antibiotic due to nausea or vomiting, development of any new symptoms. • **Call if symptoms return**. If your symptoms of UTI return after completing your antibiotic, you should contact your physician.

STRENGTH OF EVIDENCE AND RECOMMENDATION GRADING SCHEMES **Abbreviations** **Back to TOC**	
ACOG (2008)	Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force: **I** Evidence obtained from at least one properly designed randomized controlled trial. **II-1** Evidence obtained from well-designed controlled trials without randomization. **II-2** Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group. **II-3** Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

	III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees. Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories: **Level A** — Recommendations are based on good and consistent scientific evidence. **Level B** — Recommendations are based on limited or inconsistent scientific evidence. **Level C** — Recommendations are based primarily on consensus and expert opinion.
SIGN (2006)	**<u>Description of Levels of Evidence</u>** **Levels of Evidence** **1++**: High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias **1+**: Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias **1-**: Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias **2++**: High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal **2+**: Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal **2-**: Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal **3**: Non-analytic studies (e.g. case reports, case series) **4**: Expert opinion **Grades of Recommendation** **Note**: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the

	clinical importance of the recommendation. **A**: At least one meta-analysis, systematic review of randomized controlled trials (RCTs), or RCT rated as 1++ and directly applicable to the target population; *or* A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results **B**: A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1++ or 1+ **C**: A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2++ **D**: Evidence level 3 or 4; *or* Extrapolated evidence from studies rated as 2+ **Good Practice Points**: Recommended best practice based on the clinical experience of the guideline development group
UMHS (2005)	**Rating Scheme for the Strength of the Evidence** Levels of evidence for the most significant recommendations: A. Randomized controlled trials B. Controlled trials, no randomization C. Observational trials D. Opinion of expert panel

COMPARISON OF METHODOLOGY ***Click on the links below for details of guideline development methodology***		
ACOG METHODOLOGY (2008)	**SIGN METHODOLOGY (2006)**	**UMHS METHODOLOGY (2005)**

Methods used to collect/select the evidence were similar, with all three groups performing searches of electronic databases as well as hand-searches of published literature (primary sources); ACOG and UMHS also performed hand-searches of published literature (secondary sources). All three groups provide details of the literature search process, including the names of electronic databases that were searched, date range applied, and search terms used. To assess the quality and strength of the evidence, all three groups used weighting according to a rating scheme and provide the scheme. To analyze the evidence, a systematic review of the evidence was performed by all three groups (SIGN's incorporated evidence tables); ACOG and SIGN also reviewed published meta-analyses. Expert consensus was employed by all of the groups to formulate the recommendations, with ACOG and UMHS employing a rating scheme to identify the strength of the recommendations. Internal peer review was used by all three groups as a method of guideline validation and all three provide a description of the process; SIGN also utilized external peer review.

SOURCE(S) OF FUNDING Abbreviations Back to TOC	
ACOG (2008)	American College of Obstetricians and Gynecologists (ACOG)
SIGN (2006)	Scottish Executive Health Department
UMHS (2005)	The University of Michigan Health System (UMHS) provides funding for guideline development. No external funds are used.

BENEFITS AND HARMS Abbreviations Back to TOC	
Benefits	
ACOG (2008)	Accurate diagnosis and appropriate management of urinary tract infections in nonpregnant women
SIGN (2006)	• Relief of symptoms from UTI • Prevention of adverse treatments effects • Prevention of UTI recurrence • Prevention of symptom development in asymptomatic UTI patients

UMHS (2005)	• Clinical care resources are utilized appropriately and good clinical outcomes are obtained when a cost-effective strategy is used for the diagnosis and treatment of uncomplicated UTI.
	• A review of 28 treatment trials of adult women with uncomplicated cystitis concluded that no benefit was achieved by increasing the length of therapy beyond 5 days. Specific benefits of shorter course (
	  • Decreased costs of antibiotics
	  • Improved patient compliance
	  • Decreased adverse effects of antibiotic treatments (e.g., amoxicillin-associated vaginitis)
	• A recent study in Seattle examined a phone triage guideline. Use of the guideline decreased cost and increased appropriate antibiotic use without any increase in adverse outcomes.

Harms	
ACOG (2008)	Adverse events associated with antimicrobial treatment regimens (see Table 1 in the original guideline document)
SIGN (2006)	Adverse effects of antibiotic treatment
SIGN (2006)	• Side effects of antibiotic treatment include rash, nausea, diarrhea, and vaginitis. Adverse effects associated with the use of TMP/SMX increase markedly if treatment is continued past 3 days. • Fluoroquinolones increase the risk of tendon rupture in those over age 60, in kidney, heart, and lung transplant recipients, and with concomitant steroid therapy.

CONTRAINDICATIONS **Abbreviations** **Back to TOC**	
ACOG (2008)	Not stated
SIGN (2006)	• Women with renal impairment should not be treated with nitrofurantoin. • Women with LUTI, who are prescribed nitrofurantoin, should be advised not to take alkalinising agents (such as potassium citrate). • Given some antibiotics are toxic in pregnancy, refer to the British National Formulary (BNF) for contraindications, available at

	www.bnf.org.
UMHS (2005)	Quinolones are contraindicated in pregnancy.

Abbreviations
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ACOG, American College of Obstetricians and Gynecologists

ASB, asymptomatic bacteriuria

IDSA, Infectious Diseases Society of America

LE, leucocyte esterase

LUTI, lower urinary tract infection

SIGN, Scottish Intercollegiate Guidelines Network

SMX, sulfamethoxazole

STD, Sexually transmitted disease

STI, Sexually transmitted infection

TMP, trimethoprim

UA, urinalysis

UC, urine culture

UMHS, University of Michigan Health System

UTI, urinary tract infection

UUTI, upper urinary tract infection

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